Meningococcal

The prevention of meningococcal disease has been a hot topic for several years. A new vaccine is going to change the way we approach this terrible disease.

Meningococcal disease is an acute, potentially severe illness caused by the bacteria *Neisseria meningitidis*. *Neisseria meningitidis* is a leading cause of bacterial meningitis and sepsis in many parts of the world. Meningococcal disease is unique among causes of bacterial meningitis in that it causes not only sporadic disease but also outbreaks. In sub-Saharan Africa the organism causes major epidemics of meningitis and bacteremia. The World Health Organization estimated meningococcal disease was the cause of 171,000 deaths worldwide in 2000.

Neisseria meningitidis, or meningococcus, is an aerobic gram-negative bacterium, closely related to Neisseria gonorrhea, and to several nonpathogenic *Neisseria* species. Meningococci are classified into groups, called serogroups, based on the characteristics of the polysaccharide capsule. At least 13 antigenically and chemically distinct polysaccharide capsules have been described. However, most invasive disease is caused by five serogroups: A, B, C, Y, and W-135.

The relative importance of each serogroup depends on geographic location, as well as other factors, such as age. For instance, serogroup A is a major cause of disease in sub-Saharan Africa, but is rarely isolated in the United States.

Infection with *Neisseria meningiditis* can result in serious disease. The case fatality rate of invasive disease is 9% to 12%, even with appropriate antibiotic therapy and intensive medical care. The fatality rate of meningococcemia is up to 40%. Up to 20% of survivors have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb.

Even in the absence of a routine vaccination program, meningococcal disease is relatively rare in the United States, with 2 to 3,000 cases reported each year. The overall rate in the United States is about 1 case per 100,000 population, shown here in the pink line. The highest age specific rates are among infants younger than 1 year of age. Incidence declines in early childhood, increases during adolescence and early adulthood, declines among older adults, increasing again among the elderly. Although incidence is relatively low, more cases occur in persons 23 to 64 years of age than in any other age group. Although not as high as rates among infants and young children, adolescents and young adults have rates of invasive disease higher than the overall U.S. rate. In this age group the rate of invasive disease peaks at 16 to 20 years of age, then declines. It is this peak that will be the target of recommendations for the new meningococcal conjugate vaccine.

The proportion of disease caused by different serogroups has changed during the last 15 years. From 1988 to 1991, most cases of meningococcal disease in the United States were due to either serogroup C or B, and serogroup Y accounted for only 2% of cases. In 1996 through 2001, serogroup Y accounted for 21% of cases, with serogroups C and B accounting for 42% and 31%, respectively. Serogroups A and W-135 are rare causes of invasive disease in the U.S. The proportion of cases caused by each serogroup varies by age group. In 2001, about two thirds of cases among infants younger than 1 year of age were caused by serogroup B, for which no vaccine is available in the United States.

Individual risk factors for the development of meningococcal disease include deficiencies in the terminal complement pathway and functional or anatomic asplenia. Persons with HIV infection are probably at increased risk for meningococcal disease. Additional risk factors include smoking and passive exposure to smoke, upper respiratory tract infection, and crowding. In the African “meningitis belt”, an area that extends from Ethiopia to Senegal, seasonal peaks of meningococcal disease occur with rates several fold higher than in industrialized countries. In addition, epidemics occur every 8 to 12 years with attack rates of 500 to 1,000 cases per 100,000 population.

In the United States, more than 95% of cases of meningococcal disease are sporadic single cases. But meningococcal disease sometimes occurs in small outbreaks, both in the community and among organizations such as schools. Outbreaks have occurred among college students, and led to concerns that this group might be at increased risk for the disease.

In the United States, meningococcal disease is a reportable condition. Information on age is collected, but information about college attendance is not routinely collected. These are data from a 2001 publication on meningococcal disease among college age persons. It shows incidence rates among various groups of 18 to 23 year olds in 1998 and 1999. The overall incidence among 18 to 23 year olds, including those who are not college students, was 1.4 cases per 100,000 population – not much different than the overall U.S. rate. Among college freshmen, the rate was slightly higher, 1.9 per 100,000. But among college freshmen who live in dormitories, the rate was 5.1 per 100,000, more than twice as high as for all freshmen, and three times the rate for persons of the same age who do not attend college. A case control study among college students with meningococcal disease found that being a freshman living in a dormitory, white race, radiator heat, and recent upper respiratory infection were also risk factors for the disease. Interestingly, attending a movie in the prior month **reduced** the risk.

There are now two meningococcal vaccines available in the United States. Meningococcal polysaccharide vaccine, called Menomune®, has been available since 1978. Meningococcal conjugate vaccine, brand name Menactra™, was

licensed by the Food and Drug Administration in January 2005. Both vaccines are produced by Sanofi Pasteur.

Meningococcal polysaccharide vaccine – Menomune – which we will refer to as MPV, is a quadrivalent vaccine that contains the capsular polysaccharide of meningococcal serogroups A, C, Y, and W-135. As we mentioned earlier, serogroups C and Y account for about two thirds of disease in the United States. Serogroups A and W-135 are rare in the U.S. No vaccine is available for serotype B, which is responsible for about a third of meningococcal disease in this country. MPV is approved for persons 2 years and older. The schedule is one dose with selective revaccination if the person remains at risk. We will discuss revaccination in more detail in a moment. MPV is administered by subcutaneous injection.

Meningococcal polysaccharide is a T cell independent antigen, like other capsular polysaccharides. As a result, meningococcal polysaccharide vaccine is similar to other pure polysaccharide vaccines in that it is less effective in children younger than 18 months of age than among older persons. It also does not produce good immunologic memory, and the antibody that is produced is not as effective as that produced by protein antigens. Efforts have been underway for several years to develop a protein conjugated meningococcal vaccine, as was done for Hib and pneumococcal conjugate vaccines. Monovalent serogroup C conjugate vaccines have been available for several years in Europe. These vaccines have had a dramatic impact on the incidence of type C meningococcal disease in countries where it has been widely used. The first U.S. meningococcal conjugate vaccine was licensed by FDA in January 2005

The U.S. meningococcal conjugate vaccine, or MCV, is called Menactra. Like meningococcal polysaccharide vaccine it is quadrivalent and contains the same serogroups as Menomune – A, C, Y, and W-135. The polysaccharides are conjugated to diphtheria toxoid. This is an important point that we will discuss again when we talk about acellular pertussis vaccines for adolescents. MCV is approved for persons 11 through 55 years of age. It is likely that it will be approved for younger age groups in the future. The schedule for MCV is 1 dose. Unlike Menomune, MCV is administered by **intramuscular** injection. This is an important point; meningococcal conjugate vaccine is administered by intramuscular injection, not by subcutaneous injection like the polysaccharide vaccine. We have already gotten questions about management of persons who received Menactra by the incorrect route. There are no data on the subcutaneous administration of meningococcal conjugate vaccine. So **please** be sure that you and your staff understand this and administer Menactra by the correct route.

Meningococcal conjugate vaccine is supplied as a liquid in a single dose vial. The stopper of the vial contains dry natural rubber latex. The vaccine does not contain a preservative.

Meningococcal conjugate vaccine was not licensed based upon a clinical trial of vaccine efficacy as is typically done for new products. Rather, the efficacy of MCV was inferred by demonstrating that the serologic response to the vaccine was not inferior to the currently licensed polysaccharide vaccine. A similar or higher percent of persons who received MCV had a significant increase in antibody level, and similar – often higher – final titer of antibody than those of similar age who received pure polysaccharide vaccine.

At its February 2005 meeting the Advisory Committee on Immunization Practices voted to expand its recommendations for meningococcal vaccination in the United States. These recommendations were published in May 2005, and culminated more than a year of discussion. We asked Dr. Nancy Rosenstein, chief of the Meningitis and Special Pathogens Branch of the National Center for Infectious Diseases to tell us about the new recommendations and the rationale behind them.

Meningococcal disease is a serious and potentially fatal illness. Each year, there are about 2,000 to 3,000 cases reported in the United States. Even with today's medical technology, 12% of patients with meningococcal disease die. Among survivors, another 15% have long-term sequelae, such as mental retardation, hearing loss, and loss of limbs. The severity of illness, as well as the public consternation that surrounds almost every case, makes control and prevention a priority. the highest rate of meningococcal disease is among children younger than 1 year of age. However, about half of the cases of meningococcal disease occur in persons 15 years of age and older. This means that our traditional strategy of infant immunization would require many years to significantly impact this burden of disease.

Meningococcal conjugate vaccine, which i will refer to as MCV4, was licensed in January 2005 for people 11 years to 55 years of age. We believe that MCV4 will have a longer duration of immunity than the polysaccharide vaccine. In England in 2002, all children through 20 years of age were vaccinated with a serogroup C conjugate vaccine. The vaccine had a dramatic impact on nasopharyngeal carriage, which lead to what is called herd immunity. Vaccinated people were less likely to carry the bacteria in their nose and throat and transmit it to their contacts, which indirectly protects unvaccinated people. This is a characteristic of conjugate vaccines that has been seen with both *Haemophilus influenzae* type b and pneumococcal conjugate vaccines. we are not sure that MCV4 will produce the same herd immunity, especially because we will not be vaccinating so many people at once.

This graph shows the rates of meningococcal disease by single year of age from 11 years to 30 years of age. The two lines represent rates from two separate surveillance systems, but show basically the same trend. The overall U.S. rate of meningococcal disease is about 1 case per 100,000 population, shown in the pink line. In 11-year-olds to 30-year-olds, the rate of disease begins to increase at about 11 years or 12 years of age. It peaks around the age of 18 years or 19 years at about 2 cases per 100,000, about twice the overall U.S. rate. By age 21, incidence falls below the overall U.S. rate. we hope that an adolescent strategy for MCV4 will eliminate this peak. The Advisory Committee on Immunization Practices, or ACIP, has been discussing options for the use of meningococcal conjugate vaccines since early 2004. The American Academy of Pediatrics, American Academy of Family Physicians, American College Health Association, and many other groups participated in these discussions.

Because MCV4 was licensed for people 11 years to 55 years old, our first strategy is to decrease the burden of disease among adolescents and young adults. ACIP agreed early on in the process that they wanted to make a routine recommendation for adolescents. but the difficult question was at which age to make that recommendation. A vaccination recommendation at high school

entry, around age 15 has the advantage of being just before the peak incidence in the adolescent age group, so it would have a rapid impact. But vaccination only at this age would leave younger adolescents susceptible. Also, there is little infrastructure in the U.S. to deliver vaccines at this age. few existing school vaccination requirements apply to this age group.

The other option was age 11 years to 12 years. this age has definite advantages. First, the American Academy of Pediatrics already recommends a routine healthcare visit at this age, called the pre-adolescent visit. Second, many states already have existing school vaccination requirements at this age. The disadvantage of vaccination at this age is that it would be several years before these vaccinated children reached the age of peak incidence, so impact of the program would be delayed. It would take several years to protect the age groups at highest risk. The advantages and disadvantages of these strategies were debated at great length. There were very strong opinions on both sides. Ultimately, ACIP decided that they wanted to promote both strategies.

in February 2005, ACIP voted to recommend routine meningococcal vaccination at the preadolescent visit at 11 years or 12 years of age. In addition, for the next few years, ACIP recommends vaccination of a second group – adolescents entering high school, at about 15 years of age. This two-pronged approach should reduce the incidence of meningococcal disease among adolescents more rapidly. Other adolescents who wish to decrease the risk of meningococcal disease may elect to receive the vaccine. These recommendations were published in the MMWR in may 2005 and simultaneously by AAP and AAFP.

There has been much interest in the last several years in meningococcal vaccination of college students. Overall, college students are not at higher risk for meningococcal disease than people in the same age group who are not college students. It is primarily the 600,000 freshmen living in dormitories who are at an increased risk of disease. The incidence of meningococcal disease in this group is 5 per 100,000. Only children younger than 2 years of age have a higher rate of disease. in 2001, ACIP recommended that college freshmen and their parents should be informed about meningococcal disease and the meningococcal polysaccharide vaccine so they could make educated decisions about vaccination. This recommendation proved confusing for parents and students, and was difficult for colleges, health care providers and public health agencies. Because of the availability of the new, improved meningococcal vaccine as well as a consensus that a more straightforward recommendation was needed, ACIP has changed that recommendation. ACIP now recommends routine vaccination for college freshmen living in dormitories. because of the feasibility of campaign targeting, some colleges may choose to require vaccination for all matriculating freshmen. Other students may elect to receive the vaccine. In college students, the conjugate vaccine is preferred, but the polysaccharide vaccine is acceptable.

Because MCV4 is so new we do not yet have data on the duration of protection. Serogroup C conjugate vaccine were introduced in the united kingdom in 2002. Protection from that vaccine was estimated at 90% among 11-year-olds to 18-year-olds after four years. It was much lower among younger children. Based on information from England, we believe that MCV4 should provide a longer duration of protection than the polysaccharide vaccine. How much longer, we do not know. ACIP made the assumption that the conjugate vaccine will provide protection for at least eight years. So a child vaccinated at age 11 or 12 years should still be protected at least through the freshman year of college. CDC and others will be closely monitoring this for the years to come. We hope that a booster dose at college entry will not be needed.

We believe that the availability of this new vaccine will prevent many serious illnesses and deaths due to meningococcal disease. There are still a few unknowns about the vaccine, and implementation of a routine vaccination program for adolescents will be a challenge. Licensing of the meningococcal conjugate vaccine is only one step forward towards control and prevention of meningococcal disease. but it's a huge step forward.

There are now two meningococcal vaccines available in the United States, and you may need to stock them both, at least for now. Meningococcal conjugate vaccine is approved only for persons 11 through 55 years of age. Persons ages 2 through 10 years, and those older than 55 years for whom meningococcal vaccine is recommended should receive the meningococcal **polysaccharide** vaccine. Meningococcal conjugate vaccine is preferred in all cases where ACIP recommends meningococcal vaccine for persons 11 through 55 years of age. This preference is based on the immunogenicity of MCV demonstrated in prelicensure studies, as well as the knowledge that conjugate vaccines generate a stronger, longer lasting immune response than the corresponding pure polysaccharide vaccine.

ACIP recommends meningococcal vaccine for persons 11 through 55 in certain high risk groups. These groups include military recruits and certain research and laboratory personnel, particularly those who are exposed routinely to meningococci in solutions that may be aerosolized. Vaccine is also recommended for travelers to and U.S. citizens residing in countries in which *Neisseria meningitidis* is hyperendemic or epidemic, such as the central African meningitis belt and the Hajj in Saudi Arabia. Meningococcal vaccine is recommended for persons with terminal complement component deficiency, a type of immunodeficiency disease, as well as persons with HIV infection and functional or anatomic asplenia. Meningococcal conjugate vaccine is recommended for all persons at their preadolescent visit, which should occur at ages 11 or 12 years. This is also the time when most children should receive their first booster dose of tetanus- and diphtheria-containing vaccine. In order to produce the most rapid reduction of meningococcal disease in this age group ACIP also recommended that for the next 2 to 3 years teens about to enter high school also be vaccinated, at age 15 years. College freshmen living in a dormitory should be routinely vaccinated. Other adolescents who wish to reduce their risk for meningococcal disease may elect to receive vaccine. MCV is preferred for all these groups.

We receive many questions about revaccination with meningococcal vaccine. The questions are most often in the context of international travel, or persons with a medical condition that increased the risk of meningococcal disease, such as asplenia. Although there are limited data, revaccination for persons who previously received polysaccharide vaccine may be indicated for persons at high risk for infection, such as persons residing in areas in which the disease is epidemic. Providers should consider revaccination of children who were first vaccinated when they were younger than 4 years of age after 2 to 3 years, if the child remains at high risk. Although the need for revaccination of older children and adults has not been determined, antibody levels decline after 2 to 3 years, and if an indication for vaccination still exists revaccination may be considered 5 years after receipt of the first dose of MPV. For persons ages 11 through 55 years, revaccination with MCV is preferred but meningococcal polysaccharide vaccine is acceptable. We expect that MCV will provide longer protection than the polysaccharide vaccine. However, studies will be needed to confirm this. We anticipate that more data will become available within the next five years to guide

recommendations on revaccination for persons who were previously vaccinated with meningococcal conjugate vaccine. There is currently no indication for more than one revaccination dose. Continued attendance at college, or continued residence in a college dormitory is **not** an indication for revaccination in the absence of another indication, such as asplenia.

Adverse reactions following meningococcal vaccines are similar to those following other inactivated vaccines. Reactions are mostly local and are generally mild. Data from the immunogenicity trials indicates that adverse reactions are somewhat more common following conjugate vaccine than polysaccharide vaccine.

Contraindications and precautions for meningococcal vaccine are the same as those for most other inactivated vaccines. A severe allergic reaction to a vaccine component or following a prior dose is a contraindication to receipt of further doses. A moderate or severe acute illness is reason to defer routine vaccination. Immunosuppression is not a contraindication to vaccination, although the response to the vaccine may be suboptimal. We have received many questions about the use of meningococcal vaccine among women who are or may be pregnant. As with other inactivated vaccines, pregnancy is **not** a contraindication to either meningococcal polysaccharide or meningococcal conjugate vaccine. Pregnancy testing prior to vaccination is not necessary.

The new meningococcal conjugate vaccine, as well as the new recommendations for its use, are going to require a lot of education for both your staff and your clients. The ACIP statement is available to you from MMWR, or from our broadcast resources web page. There is also a revised Vaccine Information Statement that includes both polysaccharide and conjugate vaccine information available on the National Immunization Program website. One additional resource you may find useful is a patient education product available from the Vaccine Education Center at Children's Hospital of Philadelphia. They have developed another in their series of Q and A tearsheets for parents. This one is titled "Meningococcus: What You Should Know." It is available to download and print yourself, or on a pad of 50 sheets. It is available in both English and Spanish. These tearsheets will come in handy if you have adolescents in your practice. We will put a link to the Vaccine Education Center educational materials on our broadcast updates and resources website.